Decision Memo for Deep Brain Stimulation for Parkinson's Disease (CAG-00124N)

Decision Summary

Effective upon implementation of our national coverage determination, Medicare will cover *unilateral or bilateral thalamic VIM DBS* for the treatment of essential tremor (ET) and/or Parkinsonian tremor and *unilateral or bilateral STN or GPi DBS* for the treatment of Parkinson's disease only under the following conditions:

1. Medicare will only consider DBS devices to be reasonable and necessary if they are Food and Drug Administration (FDA) approved devices for DBS or devices used in accordance with FDA approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.

2. For thalamic VIM DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

3. Diagnosis of essential tremor (ET) based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form

4. Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.

5. Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

•For STN or GPi DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

•Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).

- Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.

- L-dopa responsive with clearly defined "on" periods.

- Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling "off" periods) despite optimal medical therapy.

- Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

DBS is not reasonable and necessary and is not covered for ET or PD patients with any of the following:

1. Non-idiopathic Parkinson's disease or "Parkinson's Plus" syndromes.

2. Cognitive impairment, dementia or depression which would be worsened by or would interfere with the patient's ability to benefit from DBS.

3. Current psychosis, alcohol abuse or other drug abuse.

4. Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.

5. Previous movement disorder surgery within the affected basal ganglion.

6. Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation

Patients who undergo DBS implantation should not be exposed to diathermy (deep heat treatment including shortwave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely affect the DBS system or adversely affect the brain around the implanted electrodes.

DBS should be performed with extreme caution in patients with cardiac pacemakers or other electronically controlled implants which may adversely affect or be affected by the DBS system.

For DBS lead implantation to be considered reasonable and necessary, providers and facilities must meet all of the following criteria:

1. Neurosurgeons must: (a) be properly trained in the procedure; (b) have experience with the surgical management of movement disorders, including DBS therapy; and (c) have experience performing stereotactic neurosurgical procedures.

2. Operative teams must have training and experience with DBS systems, including knowledge of anatomical and neurophysiological characteristics for localizing the targeted nucleus, surgical and/or implantation techniques for the DBS system, and operational and functional characteristics of the device.

3. Physicians specializing in movement disorders must be involved in both patient selection and post-procedure care.

4. Hospital medical centers must have: (a) brain imaging equipment (MRI and/or CT) for pre-operative stereotactic localization and targeting of the surgical site(s); (b) operating rooms with all necessary equipment for stereotactic surgery; and (c) support services necessary for care of patients undergoing this procedure and any potential complications arising intraoperatively or postoperatively.

Since long-term safety, effectiveness and optimal targeting for DBS have not been established, CMS will review the appropriateness of Medicare coverage as pertinent new evidence becomes available. This review will include clinical follow-up and targeting information from the ongoing, randomized VA/NINDS Cooperative Trial comparing best medical therapy with DBS of the STN and GPi for PD, as well as longer term clinical results from mandatory annual progress reports and final report to the FDA of Medtronic's bilateral DBS PMA postapproval study.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

TO: Administrative File CAG: #00124N Deep Brain Stimulation (DBS) for Parkinson's Disease

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SUBJECT: National Coverage Determination Memorandum for Deep Brain Stimulation for Essential Tremor and Parkinson's Disease

DATE: February 6, 2003

This memorandum serves four purposes: (1) outlines the description of Deep Brain Stimulation (DBS) for Essential Tremor and Parkinson's Disease; (2) reviews the history of Medicare's national coverage policies on DBS; (3) presents and analyzes the relevant clinical and scientific data related to the use of DBS; and (4) delineates the reasons for announcing our intent to issue a national coverage determination for this therapy under certain conditions.

Clinical Background

Essential tremor and Parkinson's disease are the two most common movement disorders.

Essential tremor (ET) is a progressive, disabling action tremor (also referred to as a kinetic or postural tremor) which most often affects the hands during sustained arm extension or during voluntary motion such as writing or pouring. ET may also affect the head, voice and legs and it is estimated to affect more than 1 million patients in the U.S. Although ET may start at any age, there appears to be a bimodal distribution peaking in the second and sixth decades. ET affects men and women equally and while its precise pathogenesis is unknown, it does occur genetically in some families as an autosomal dominant trait.

Pharmacotherapy with propanolol (a beta-adrenergic blocker) and primidone (an anticonvulsant medication) are first line agents in the treatment of ET and may improve function by reducing the severity of tremor. However, certain patients do not adequately respond to or cannot tolerate these medications. Thalamic DBS may be helpful for carefully selected individuals with marked tremor causing significant functional disability who are refractory to optimal medical therapy.

Parkinson's disease (PD) is an age-related neurodegenerative disorder, characterized by tremor, rigidity, bradykinesia (gradual loss of spontaneous movement) and progressive postural instability. PD effects up to 1 million Americans. The primary underlying abnormality in PD is the progressive loss of dopamine-producing cells in the brain, leading to an imbalance of dopamine and acetylcholine, the normal neurotransmitters in the corpus striatum. The most common form, idiopathic PD, begins most often between ages 45-65, with average onset at age 58. The cause of PD remains unknown, although proposed theories include the role of genetic and certain environmental factors.

Treatments for PD include those which alleviate symptoms (symptomatic therapy), slow the loss of nerve cells (neuroprotective), and increase and/or improve cell function (restorative). Currently, symptomatic therapy - with medications, lesioning surgery or DBS - is the only available treatment for patients with PD. While neuroprotective and restorative therapies are in various stages of development, neuroprotection has yet to be demonstrated by any currently used therapeutic agent. Restorative therapy with fetal tissue implants or other grafts remains experimental.[1]

Dopamine itself is ineffective for treatment because it is unable to cross the blood-brain barrier. Levodopa (L-dopa), which can cross the blood-brain barrier, is dopamine's immediate metabolic precursor and is converted to dopamine in the brain. L-dopa is the oldest and most potent symptomatic drug treatment and remains the gold standard for relieving the symptoms of PD. However, significant side effects may occur and include dyskinesias, motor fluctuations, and disabling periods of rigidity.

In practice, L-dopa is often administered in combination with carbidopa (Sinemet) to prevent the metabolism of L-dopa in the peripheral tissues, thereby reducing the dose of L-dopa and reducing side effects. Dopamine agonists (such as bromocriptine, pergolide, pramipexole and ropinirole), which directly stimulate dopamine receptors but are not as effective as L-dopa, are also used as an initial form of therapy in order to delay the need for L-dopa and its associated long-term adverse effects.

After 5 to 10 years of drug therapy it is often increasingly difficult to balance the control of PD symptoms with the adverse effects of these dopaminergic medications. For patients who become unresponsive to pharmacological treatments and/or have intolerable drug side effects, lesioning surgeries and DBS may be helpful for carefully selected patients. Lesioning surgeries, including thalamotomy and pallidotomy, have been treatments for Parkinson's disease for over 40 years and are based on precise localization and reduction of overactivity in the target nuclei of the brain. The creation of a small ablative lesion in the thalamus (thalamotomy) or in the globus pallidus interna (pallidotomy) involves neurosurgical insertion of an electrode into the thalamus or globus pallidus interna (GPi), heating of the tip of the electrode to result in a small area of necrosis in the target nucleus and subsequent removal of the electrode. Thalamotomy has been shown to be substantially effective for tremors, while pallidotomy potentially alleviates other symptoms of PD. Associated morbidities with these procedures, which include speech disturbances, dysequilibrium and cognitive dysfunction, severely limit their applicability. This is particularly the case for patients with bilateral symptoms.

DBS requires the stereotactic placement of an indwelling electrode in the brain. This treatment for PD is supported by observations that high-frequency stimulation of the affected neurons induces functional inhibition in target regions of the brain. DBS thus simulates the effect of a ablative surgical lesion but, unlike lesioning surgery DBS can be adjusted (or turned off) and the implanted electrode can be re-positioned (or removed). The mechanism of action remains unknown. Possible mechanisms include release of local inhibitory neurotransmitters, depolarization blockade, or jamming of abnormal neuron firing patterns.

The device currently used for DBS is the Activa® system developed by Medtronic, Inc. (Minneapolis, MN).[2] The system consists of several implantable and nonimplantable components (listed below), including a quadripolar electrode (four contact sites arranged along the distal edge) which is stereotactically implanted into the targeted structure. Stimulation parameters, including electrode contact site selection, stimulation pulse amplitude, frequency, and width are then adjusted to optimize symptom relief.

Implantable components:

- Neurostimulator (a small, sealed device implanted beneath the skin in the chest);
- DBS™ Lead (a thin, insulated wire with 4 electrodes at the tip, implanted in the brain);
- Lead extension (a thin, insulated wire implanted under the skin of the head and neck, connecting the lead to the neurostimulator)

Nonimplantable components:

- Physician Programmer with MemoryMod software cartridge (to allow the system to be noninvasively adjusted);
- Handheld patient therapy controller

The overall DBS procedure consists of the following basic segments:

- Stereotactic image acquisition and coordinate calculation, using computed tomography (CT) or magnetic resonance imaging (MRI);
- Under local anesthesia, stereotactic neurosurgical creation of a burr hole and passage of a probe through brain tissue to the target, followed by implantation of the DBS electrode, with intraoperative stimulation to ensure the absence of significant adverse effects;
- Under general anesthesia, surgical tunneling of the lead extension wires (from the scalp to the upper chest area) and implantation of pulse generator in the chest wall, followed by programming of the stimulator

FDA Status

In July 1997, the FDA approved with conditions the PMA for Medtronic's Activa® Tremor Control System.[3] Indications for use are:

“Unilateral thalamic stimulation by the Medtronic Activa Tremor Control System is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with Essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.”

In January 2002, the FDA approved with conditions the PMA supplement for Medtronic's Activa® Parkinson's Control Therapy System.[4] Indications for use are:

“Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic Active Parkinson's Control Therapy is indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication.”

Benefit Category Determination

For an item or service to be covered by the Medicare program it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. DBS for Parkinson's disease is covered under the following statutorily defined benefit categories:

§1861(s)(1) physician services
§1861(s)(8) prosthetic device

History of Medicare Coverage

An existing national noncoverage policy for the treatment of motor function disorders with electric nerve stimulation is detailed in CIM section 35-20 (Treatment of Motor Function Disorders with Electric Nerve Stimulation - Not Covered). In March 1997, CMS amended this policy to note that:

"Medicare coverage of deep brain stimulation by implantation of a stimulator device is not prohibited. Therefore, coverage of deep brain stimulation provided by an implanted deep brain stimulator is at carrier's discretion."

Timeline of Recent Events

On August 17, 2001, CMS received a letter and a packet of information, including scientific literature, from Barry Green, Ed.D., of Dallas, TX, requesting that the Coverage and Analysis Group (CAG) review bilateral STN stimulation for Parkinson's disease for a Medicare national coverage determination. CMS staff worked with Dr. Green to complete this formal request, including gathering the appropriate evidence, and formally accepted his request for review.

October 19, 2001	Initiation of formal review process and timeline posted on CMS website.
December 13, 2001	CMS requested that the Agency for Healthcare Research and Quality (AHRQ) purchase a technology assessment of bilateral deep brain stimulation of the STN or the GPi for treatment of advanced Parkinson's disease recently performed by the Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC).

January 7, 2001	CMS expanded its evaluation of the evidence to include DBS for essential tremor and Parkinsonian tremor. The title of this determination was changed to "Deep Brain Stimulation for Parkinson's Disease."
March 8, 2002	Issue was referred to the Medicare Coverage Advisory Committee (MCAC), Medical and Surgical Procedures Panel.
June 12, 2002	MCAC Medical and Surgical Procedures Panel held in Baltimore, MD.
September 25, 2002	MCAC Executive Committee (EC) meeting held in Baltimore, MD.
November 1, 2002	MCAC EC minutes received by CMS.

General Methodological Principles of Clinical Study Design

There are several generally accepted methodological principles CMS uses when assessing a clinical trial. For example, we evaluate whether or not the method in which a study selected patients, including inclusion and exclusion criteria, was described, as well as whether steps were taken to assure randomization (when appropriate) and comparability of the experimental and control groups. Also of importance are the methods in which health outcomes of study participants were assessed, specifically the masking of patients and investigators to the therapy administered, and whether appropriate statistical analyses were performed.

Measures of Clinical Treatment Outcomes for Essential Tremor and Parkinson's Disease

The evidence to be reviewed below will include frequent references to standard measures of extent of disease in ET and PD. This section will attempt to familiarize the reader with those scales.

The Clinical Tremor Rating Scale (CTRS), which includes ratings of tremor amplitude, functional ability and social activities, is probably the most widely used standardized instrument for the evaluation of ET. Graded tremor severity is rated from none to severe using a five point scale where 0 = none, 1 = slight, 2 = moderate, 3 = marked and 4 = severe tremor in the limb intended for treatment.[5]

Measures of clinical outcomes for treatment of Parkinson's disease consist of various standardized tests, including the **Unified Parkinson's Disease Rating Scale** (UPDRS), the **Schwab and England scale**, the **Hoehn and Yahr scale**, scales developed for the **Core Assessment Program for Intracerebral Transplantations** (CAPIT), and tests quantifying tremor and dyskinesia.

The UPDRS is the most widely used instrument for the evaluation of Parkinson's disease. It consists of a comprehensive inventory of symptoms and signs of Parkinson's disease divided into four subscales: 1) mentation, behavior and mood; 2) activities of daily living (ADLs); 3) motor examination; and 4) complications of therapy such as dyskinesias (abnormal involuntary movements) and clinical fluctuations in “on” and “off” periods. Scores for the total inventory range from 0 (normal) to 176 (worst possible). “On” periods are times when the patient experiences a good response to antiparkinsonian medication, i.e., experiences good mobility and dexterity. “Off” periods are times when a patient's parkinsonian symptoms become worse, i.e., the patient experiences immobility and loss of dexterity, due to a temporary loss of medication effect or prolonged withdrawal of medication.

Patients are assessed at two intervals. The first state is referred to as the “off” medication state, which is that condition observed after a patient has received no antiparkinsonian medications for 12 hours. This testing is typically conducted before the patient has taken his or her first morning dose of L-dopa and is intended to replicate the severity of symptoms patients experience in their daily lives as L-dopa becomes less effective and motor fluctuations become more frequent and severe. The “on” medication state is defined, by convention, as the best test scores recorded during the day while the patient is taking L-dopa. In some studies, “on” scores are measured during a “best on” state created with a suprathreshold dose of L-dopa.

The Schwab and England scale is an instrument designed exclusively to evaluate performance of activities of daily living. Scoring direction is the reverse of the UPDRS: a score of 100 indicates normal and a score of 0 indicates complete disability. Like the UPDRS, the Schwab and England scale is usually measured in the “off” and “on” states.

The Hoehn and Yahr scale is a measure of a patient's PD state, with disease stages ranging from 0-5 as follows:

- Stage 0: no signs of disease
- Stage 1: unilateral disease, no imbalance
- Stage 2: bilateral disease, no imbalance
- Stage 3: mild to moderate bilateral disease
- Stage 4: severe disability, still able to walk or stand unassisted
- Stage 5: wheelchair bound or bedridden

Evaluation of neuropsychological sequelae of DBS requires a special battery of assessment instruments selected for their minimal dependence on motor function. Evaluation must be conducted in a manner that minimizes such variables as fatigue and motor symptoms, at a standard time of day when patients are in their best state. Understanding of these evaluations may be further improved by application of statistical techniques for analyzing longitudinal, repeated measures.

Unilateral and Bilateral Thalamic (VIM) DBS Evidence Summary

1997 BCBSA Technology Evaluation Center (TEC) Technology Assessment

The BCBSA TEC evaluated DBS of the thalamus for tremor in December 1997.[6] This technology assessment was based on the published literature for patients undergoing implantation of a thalamic stimulation device throughout Europe and North America. Nine studies met study selection criteria (studies must have presented original data, included more than one subject, examined health outcomes, and be published as full-length articles in peer-reviewed journals). The most recently published series from each research group were discussed by BCBSA TEC and are subsequently described in this decision memo.[7,8,9] Evidence from the Medtronic Global Clinical Study Series (1992-1997) was also discussed by TEC but was excluded from TEC's outcomes analyses since some patients in the Medtronic series had already been published separately in the studies described above.

Koller et al (1997) conducted a multicenter trial, involving four clinical sites, of unilateral thalamic (VIM) DBS in 29 ET patients and 24 PD patients with tremor of marked severity resulting in significant disability despite pharmacological treatment. Mean age was 66.8 years for ET patients and 65.4 years for PD patients. ET was diagnosed by postural or kinetic tremors of the hands without other neurologic signs. The diagnosis and selection criteria for PD patients included the presence of 2 cardinal signs (tremor, bradykinesia, rigidity) plus sustained responsiveness to L-dopa and absence of signs of other parkinsonian syndromes. Fifty-three of 59 patients received implantation in the VIM. Six patients were not implanted or not followed, including 2 whose tremor was not suppressed by intraoperative stimulation, 1 intracranial hemorrhage during surgery, 1 persistent microthalamotomy effect, 1 subdural hemorrhage and 1 withdrawal of consent. The study's primary outcome was tremor suppression evaluated with the Tremor Rating Scale for ET and the UPDRS for PD. Patients were blinded to stimulation on or off at 3 months after surgery and with open-label (nonblinded) follow-up evaluations at 6, 9 and 12 months.

With stimulation on, there was significant decrease in contralateral tremor for ET and PD patients at each evaluation (3, 6, 9 and 12 months), with 9/29 (31%) of ET patients and 14/24 (58%) of PD patients experiencing total tremor resolution. Among secondary functional outcomes, motor performance skills significantly improved at 3 months only in the ET patients. Subjective assessment of global disability showed moderate to marked improvement in 71% of ET and 90% of PD patients.

Benabid et al (1996) reported on 117 consecutive patients with severe tremor, including 80 PD and 20 ET patients implanted with unilateral or bilateral thalamic (VIM) electrodes from 1987 through 1994. Mean age of patients, duration of illness and statistical analyses were not reported. Results indicated that tremor was the only symptom significantly influenced by thalamic (VIM) DBS, that rigidity was only slightly affected due to the tremor suppression, and that there was almost no change in bradykinesia or other symptoms of PD. During the initial 3-month postoperative period, there was either complete disappearance or only rare reappearance of tremor in 102 (91.9%) of the 111 operated sides. The effect of VIM stimulation remained stable in 96% of stimulated sides in PD and in 81% of stimulated sides in ET.

In PD patients, tremor was selectively suppressed for as long as 8 years. In ET patients, results were satisfactory but deteriorated over time in 18.5% of cases. 31.6% of patients experienced minor postoperative side effects, but there was no operative mortality or permanent morbidity. Neither simultaneous bilateral thalamic implantation performed in 38 PD and 13 ET patients, nor complementary implantation on the contralateral side of a previous contralateral thalamotomy performed in 8 PD and 2 ET patients, induced any of the neuropsychological deficits reported for bilateral thalamotomy.

Alesch et al (1995) reported on 23 idiopathic PD and 4 ET patients treated with thalamic (VIM) DBS for medically refractory tremor severely impairing most routine activities. Mean age was 65 years and mean duration of illness was 13 years. Five PD patients had previous thalamotomy more than 5 years before with sustained success. The study's primary outcome was tremor suppression evaluated by the UPDRS and the Essential Tremor Rating Scale measured preoperatively and repeated at 3, 6 and 12 months postoperatively. Twenty-seven patients were implanted unilaterally and 6 patients bilaterally, for a total of 33 operated sides.

Tremor suppression was complete in 21/33 (64%) of implanted thalami and showed major improvement in 6/33 (18%), minor improvement (marked but less pronounced tremor remaining) in 4/33 (12%) and no improvement in 2/33 (6%). Using the UPDRS subscales, patients undergoing stimulation also showed a mean improvement of 45% on the ADL score and an improvement of 43% on the motor score. There was one intraoperative subdural hematoma, one ischemic infarct and no infections. Neurostimulation side effects included permanent paresthesias in two patients, plus dysequilibrium in one, slight dysarthria in four and marked dysarthria in two patients. Within that last category, one of six patients implanted bilaterally experienced marked but reversible dysarthria under stimulation, which was directly proportional to the stimulation voltage. Despite this side effect, the patient preferred dysarthria to tremor. Study follow-up ranged from 3-48 months and reported improvements were durable in all cases.

Medtronic's Global Clinical Study Series was presented to the FDA Neurological Devices Panel in March 1997 and was summarized briefly by BCBSA TEC. In that multicenter study of 347 patients undergoing implantation of 406 DBS systems, 12% of patients experienced complications attributed to the device and 17% of patients experienced complications related to the surgical procedure. Thirteen (4%) of the 347 patients had intracranial hemorrhage, including five serious hemorrhages and one postoperative death. Of the 145 (61 ET and 84 PD) of the 347 patients followed for 12 months or more after implantation, over 80% experienced sustained tremor suppression.[10]

TEC determined that unilateral thalamic DBS for patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease met the following five criteria: 1) the technology had final approval from the appropriate government regulatory bodies; 2) the scientific evidence permitted conclusions concerning the effect of the technology on health outcomes; 3) the technology improved the net health outcome; 4) the technology was as beneficial as any established alternatives; and 5) the improvement was attainable outside the investigational settings.[11]

CMS Supplemental Review

CMS reviewed the existing literature and performed an updated search of studies published since 1997 regarding thalamic stimulation for essential or Parkinsonian tremor. Inclusion criteria included all studies reviewed as part of the December 1997 BCBSA TEC technology assessment, as well as studies identified in a PubMed database search using keywords “Parkinson*” and “deep brain stimulation”. CMS's search was restricted to English language publications and human studies with at least 10 subjects. Reference lists of retrieved publications were additionally reviewed. As noted by the TEC, several studies seemed to evaluate patients included in previously published literature. Therefore, CMS's descriptions of unilateral thalamic stimulation studies were restricted to only the most recently published studies. Sixteen studies were identified for review and are summarized in Appendix A. Among those 16 studies, two large multicenter series (published since the 1997 BCBSA TEC assessment) described symptomatic improvement of tremor in both PD and ET patients treated with unilateral and bilateral thalamic (VIM) DBS.[12,13]

Krauss et al (2001) conducted a multicenter trial of unilateral and bilateral thalamic (VIM) DBS in 94 patients with disabling tremor, including 45 PD and 42 ET patients (plus 7 patients with kinetic tremors of different causes). Electrodes were implanted unilaterally in 65 patients and bilaterally (either simultaneously or staged) in 29. Mean age was 68.7 years. Mean duration of disease and prior surgeries were not reported. The study's primary outcome was improvement in tremor assessed by a standard protocol including the UPDRS for PD patients and the Unified Tremor Rating Scale or modified Clinical Tremor Rating Scale (CTRS) for ET patients. The mean follow-up period was 11.9 months (range 3-24 months).

In PD patients, symptomatic improvement in tremor at the last available follow-up was rated as excellent in 51%, marked in 36%, moderate in 11% and minor in 2%. In ET patients, results indicated symptomatic improvement in tremor rated as excellent in 57%, marked in 36%, moderate in 5% and minor in 2%. Forty of 94 patients experienced stimulation-related side effects which were generally mild and reversible with a change in electrical parameters. These were more frequent in bilateral (52%) than unilateral (31%) DBS patients. There was no persistent morbidity related to surgery and there were no infections.

Limousin et al (1999) reported on a 12 month follow-up of 73 idiopathic PD and 37 ET unilaterally or bilaterally implanted thalamic (VIM) DBS patients with pharmacotherapy resistant tremor operated on in 13 European neurosurgical centers. The selection of patients was limited to those whose tremor scale rating was marked or severe for the limb intended for treatment and those capable of abiding by the protocol and operating the stimulator. Patients were excluded from the study if they had a previous thalamotomy on the implanted sided, significant brain atrophy or structural damage seen on CT or MRI, marked cognitive dysfunction, active psychiatric symptoms, or concurrent neurological or other uncontrolled medical disorders. In PD patients, mean age at implant was 61.5 years and mean duration of disease 10 years. Fifty-seven PD patients were implanted unilaterally and 16 bilaterally. In ET patients, mean age at implant was 63.1 years and mean duration of disease 26.6 years. Twenty-eight ET patients were implanted unilaterally and 9 bilaterally.

Results indicated that both upper and lower limb tremor were significantly reduced in PD patients at 3 and 12 month follow-up. In ET patients, stimulation significantly reduced postural and action tremor of the upper and lower limb at 3 and 12 months, but head tremor was significantly improved only at 3 month follow-up. The number of patients using medications was not changed and the mean medication doses were not significantly reduced at 12-month follow-up. 4 patients had major adverse events unrelated to surgery (3 deaths and 1 stroke), 3 patients had subdural hematomas which resolved, 2 patients had subcutaneous hematomas which were evacuated, 2 patients had infections requiring temporary explantation, and 5 patients required electrode replacement and repositioning. Other adverse effects, including dysarthria (7), disequilibrium (3) and dystonia (1) were mild and reversible with change of stimulation parameters.

Also among the 16 studies in Appendix A is a relevant comparison of unilateral and bilateral thalamic DBS published since the 1997 BCBSA TEC assessment. In this study, Ondo et al (2001) reported on 13 ET and 8 tremor-dominant PD patients who underwent staged bilateral thalamic (VIM) DBS. Study outcomes compared both efficacy and adverse events 3 months after initial thalamic DBS implant with those 3 months after contralateral thalamic DBS placement.[14] Mean age was 71.5 years for ET patients and 71.4 years for PD patients. All ET patients and 6 of 8 PD patients elected to initially have their dominant side implanted. The ET evaluation included subjective questions based on the Unified Tremor Rating Assessment, clinical assessments of arm, leg, voice, head, face and tongue tremors, as well as drawing, writing and water pouring tests on both sides. PD patients were primarily evaluated with the UPDRS.

After the second thalamic implantation, overall results indicated all specific measures assessing tremor contralateral to that side improved in both ET and PD patients, generally without sacrificing the improvements to the first side implanted. Midline tremors of the face and head improved only after the second implantation. PD patients had less subjective improvement than ET patients in their functional and subjective scores after the second implantation, but the authors noted their relatively small sample size, short period of evaluation and inability to control for disease progression. Adverse events were described as generally mild to moderate, but more frequent in ET patients (92%) than PD patients (50%) and more frequent in bilateral (76%) than unilateral (52%) implantation. The most problematic stimulation-related adverse effects were gait disorders and dysarthria. There were no serious perioperative adverse effects.

Unilateral and Bilateral Subthalamic Nucleus (STN) and Globus Pallidus Interna (GPi) DBS Evidence Summary

The largest clinical series of bilateral DBS was a multicenter study by the "Deep Brain Stimulation for Parkinson's Disease Study Group (DBSPDG)." This study reported on 143 patients enrolled at 18 centers (including 4 within the U.S.) between July 1995 and July 1999.[15] Of note, evidence presented to the March 2000 FDA Neurological Devices Advisory Committee reported on 159 patients enrolled in this study.[16,17,18,19] Assignment to either bilateral STN or GPi DBS was according to the operating neurosurgeon's preference and not all centers performed both STN and GPi procedures. Patients ages ranged from 30-75 years and each patient had at least 2 cardinal features of Parkinsonism (tremor, rigidity and bradykinesia), a good response to L-dopa, a motor score of >30 on the UPDRS when off medication, and motor complications that could not be controlled by pharmacologic therapy. Mean age at surgery was 59.6 years for STN patients and 55.7 years for GPi patients. Nine of the 143 patients enrolled (6 in the STN group and 3 in the GPi group) did not receive bilateral DBS because of complications in the initial unilateral DBS implantation, including intracranial bleed, paresis, confusion, lack of response to DBS and improper lead placement.

Analysis of the 134 patients bilaterally implanted excluded 5 of 102 patients in the STN group who did not participate in the 3 month blinded evaluation or the 6 month follow-up (2 with infected leads and 3 who withdrew consent), excluded 3 of 41 patients in the GPi group who did not participate in the 3 month blinded evaluation (2 refused and 1 withdrew), and also excluded an additional 2 of 41 patients in the GPi group who did not complete 6 month follow-up (1 withdrew and 1 died of esophageal carcinoma). The DBS Study Group thus evaluated 126 of 134 bilaterally implanted patients in blinded 3 month motor assessments and 127 patients in unblinded 6 month self-reported home diary assessments. Considering omission of slightly greater than 10% of the 143 patients enrolled in this study (or slightly greater than 20% of the 159 patients reviewed by the FDA panel), the DBS Study Group's lack of intention-to-treat analysis may have resulted in an overestimation (or underestimation) of their primary and secondary outcomes.

The DBS Study Group's primary outcome was mean improvement in patients' UPDRS motor subscores after having received two hours of deep brain stimulation. Patients were assessed at 3, 6 and 12 months postoperatively. The randomization was to whether stimulation was "on first, then off" or "off first, then on" prior to measurement, and only at the 3-month assessment were patients and observers blinded to whether or not the stimulator was turned on or off. Stimulation was associated with a mean improvement in UPDRS motor subscores of 43% in the STN group and 32% in the GPi group compared to evaluation performed without stimulation. There was median improvement of greater than 25% in the UPDRS motor subscores at 15 of 16 centers performing the STN procedure and at 9 of 10 centers performing the GPi procedure. Unblinded secondary outcomes included the percent time in waking hours with poor mobility ("off" state) versus good mobility ("on" state) either with or without dyskinesias (involuntary movements). These were recorded in a home diary at the preoperative baseline and at 1, 3 and 6 months postoperatively. Between the pre-op baseline and 6 month follow-up, the self-reported improvement in the percent time with good mobility in the "on" state without dyskinesia increased from 27% to 74% for the STN group and from 28% to 64% for GPI group. Results and complication rates were not stratified by age or center. Among the DBS Study Group's 143 patients, serious adverse events included 7 intracranial hemorrhages, 4 infections (including 2 lead removals), 5 lead migrations and 4 persistent neurologic deficits. Total adverse events were not reported by the DBS Study Group. For all 159 patients reviewed by the March 2000 FDA advisory committee, 87.4% of patients experienced one or more adverse events (ranging from minor device related complications to major intracranial hemorrhage) and 52.2% of patients experienced one or more serious adverse events.[20]

2002 BCBSA TEC Technology Assessment

CMS obtained a technology assessment of bilateral DBS of the STN or the GPi for treatment of advanced Parkinson's disease performed by the BCBSA TEC. The full text of this assessment, posted in February 2002, is available on CMS's website.[21] The BCBSA TEC assessment referenced 117 articles in its review. Search methods and study selection are available in the full text.

Evidence Summary for Bilateral STN DBS

Fourteen published studies examining bilateral STN DBS met the BCBSA criteria. Among the included studies was the one large multicenter study by the DBS Study Group[22] discussed above and one large case series of 110 STN DBS patients by Benabid and colleagues from Grenoble, France.[23] The remaining 12 reports consisted of smaller, single-center studies of fewer than 25 patients. With the exception of a small pilot study of 10 patients utilizing a prospective, randomized, double-blind trial design,[24] all studies (including the DBS Study Group) consisted of retrospective case series.

While it is unknown whether patients at various study centers had similar disease severity, it was notable that all studies used similar selection criteria requiring a diagnosis of idiopathic Parkinson's disease, a response to L-dopa, and disabling motor fluctuations and/or dyskinesia despite all drug therapy. The mean age of patients in the study cohorts at the time of implantation ranged from 53 to 67 years. Follow-up duration in the majority of reports was from 6 to 12 months and ranged from 3 to 60 months.

Key outcomes for advanced PD patients focused primarily upon the disabling motor symptoms associated with either complications of medical therapy (motor fluctuations or dyskinesias) or loss of the effect of L-dopa (increasing “off” period duration and severity). Evidence is subsequently summarized from the assessment for the broad key outcomes of bilateral STN DBS, as well as for the reduction in cardinal symptoms (tremor, rigidity and bradykinesia) during “off” periods and for the duration of treatment effect.

1) Changes in motor fluctuations and duration of “off” periods

DBS of the STN was consistently associated with reduction in fluctuations of motor function, as well as reduction in percentage of waking hours spent in the “off” condition and reduction in the duration of “off” periods. In the DBS Study Group, home diaries indicated that at 6 months after surgery the percentage of time spend with poor mobility decreased from 49% of waking hours prior to implantation to 19% of waking hours with DBS stimulation. Similarly, waking time spent in an immobile “off” state decreased by as much as 50-90% in the other studies.

2) Improvement in motor function and ADLs in the “off” condition

In all 14 studies, the “off” medication motor performance improved during DBS stimulation. The DBS Study Group reported a mean UPDRS motor subscore improvement of 43% ($p<0.001$) among 51 patients evaluated 3 months postoperatively in the blinded crossover comparison of stimulator-on versus stimulator-off in the “off” medication condition. In the same trial, unblinded evaluation of 91 patients at 6 months showed continued statistically significant improvement with mean UPDRS motor subscores improved 51% compared to preoperative baseline subscores ($p<0.001$). Smaller studies demonstrated similar findings with improvements measured by UPDRS motor subscores ranging from 34-74%.[25,26]

Similarly, activities of daily living (ADLs) in the off-medication condition, as measured by UPDRS subscores, Schwab and England scales and Hoehn and Yahr scores, showed statistically significant improvement during stimulation in the nine studies examining ADL outcomes. Among 91 DBS Study Group patients, the mean UPDRS ADL score improved 44% compared to preoperative baseline in unblinded evaluation at 6 months. Benabid and co-workers' 51 patients recorded UPDRS ADL subscore improvements of 58-64% at one year.[27]

3) Improvement in motor function and levodopa -induced dyskinesias in the “on” condition

Smaller, but often significant, motor benefits were reported in the “on” medication state in some but not all studies. The DBS Study Group found that motor scores improved more than 26% with stimulation during “on” medication periods. This represented significant improvement ($p<0.001$) compared to baseline motor scores.

Bilateral STN DBS had a dramatic effect during “on” periods and provided clinically significant relief particularly from levodopa-induced dyskinesia. That complication often prevents patients from taking a therapeutic dose of L-dopa and consequently impairs the quality of those hours during which L-dopa would otherwise relieve patients of parkinsonian motor symptoms. Among 91 patients in the DBS Study Group, STN stimulation improved dyskinesia scores from a mean of 1.9 at baseline to 0.8 at 6 months ($p<0.001$). Benabid et al likewise reported 50-100% reductions in dyskinesia duration, dyskinesia disability and morning dyskinesia dystonia scores. There is debate, however, about whether the effect of bilateral DBS of the STN upon dyskinesia should be attributed to a direct effect of stimulation or to lowered L-dopa doses.

4) Reduction in daily L-dopa dosage

In all studies in which postoperative change in L-dopa dosage was reported, bilateral STN DBS permitted significant and sometimes dramatic reductions in daily L-dopa dosage. Mean dosage reductions range from 40-80%. In the DBS Study Group, mean daily L-dopa dosage decreased from approximately 1200 to 760 mg per day at 6 months ($p<0.001$). Benabid and colleagues described postsurgical L-dopa dosage reductions of 60% or more among 30 patients at 2 year follow-up and about 10% of patients in their study no longer took any L-dopa.

5) Reduction in cardinal symptoms

Severity of the cardinal symptoms of PD (tremor, rigidity, bradykinesia) during “off” periods was reduced by STN DBS. When specific symptoms were examined in the “off” medication state, stimulation of the STN had the greatest effect upon tremor, reducing it by 80% or more in most studies (with a range from 63-100%). Improvements of lesser magnitude were observed during stimulation in the “off” medication state upon rigidity (ranging from 50-75%) and upon akinesia/bradykinesia (ranging from 43-69%). In the DBS Study Group trial, reductions in “off” medication UPDRS scores for tremor, rigidity, bradykinesia and gait disturbance were significant ($p<0.001$) for each symptom in the unblinded evaluation of 91 patients 6 months after DBS implantation.

6) Duration of DBS treatment effect

The effect of STN DBS appeared to be durable for at least 1 to 3 years. Among 82 patients followed-up for a year or more, reported improvements in “off” period motor scores were clinically significant and stable over at least a 12-month period. In Benabid's study in Grenoble, 51 patients followed-up for 1 to 3 years maintained a mean “off” UPDRS motor subscore improvement of 61%.[28] Four patients in this group were followed-up for 5 years, but after 5 years of stimulation, progressive deterioration of postural stability was noted. Nine patients treated with bilateral DBS of the STN in Spain, who were followed for 3 years, experienced no loss of DBS therapeutic benefit in motor function.[29]

Evidence Summary for Bilateral GPi DBS

Nine published articles examining bilateral GPi DBS met the BCBSA criteria. There was overlap, however, among study center participants in the two included multicenter studies, with three of the five centers' patients (Toronto, Canada; Grenoble, France; and San Sebastian, Spain) reported in the Kumar study also included within the DBSPDSG.[30,31] The remaining seven studies were small trials, each with fewer than 12 patients. Evidence from the nine studies provided outcomes data for GPi DBS among at least 53 patients. Eight of the nine studies were non-randomized, open-label clinical series. As noted previously in the STN evidence section, only one small study randomized 10 patients prospectively to DBS of either the STN or the GPi.[32]

All studies required that patients have a diagnosis of advanced idiopathic Parkinson's disease, a continued response to L-dopa, and medication-induced complications, such as motor fluctuations and dyskinesia. Criteria for exclusion in the large DBS Study Group were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of a cardiac pacemaker and previous intracranial surgery. The 53 GPi DBS patients ranged in age from 38 to 69 years and their duration of follow-up ranged from 3 to 24 months.

Key outcomes for advanced PD patients focused primarily upon disabling motor symptoms associated with either complications of medical therapy (motor fluctuations or dyskinesias) or loss of the effect of L-dopa (increasing “off” period duration and severity). Utilizing the same format as the preceding section, evidence is subsequently summarized for the broad key outcomes of bilateral GPi DBS, as well as for the reduction in cardinal symptoms (tremor, rigidity and bradykinesia) during “off” periods and for the duration of treatment effect.

1) Changes in motor fluctuations and duration of “off” periods

Five studies reported mixed results about the effect of GPi DBS upon motor fluctuations and duration of “off” periods. Four small case series, each with no more than 6 patients, reported decreases in daily time spent in the “off” state, no change, or a net loss of “on” time. The DBS Study Group, evaluating 36 bilateral GPi DBS patients, reported the percentage of time with good mobility without dyskinesia to have been increased from 28% of the waking day prior to implantation to 64% with GPi DBS stimulation ($p<0.001$) after implantation.

2) Improvement in motor function and ADLs in the “off” condition

All but one study reported improvement in motor function in the “off” state with GPi DBS. The mean UPDRS motor subscores improved by 31-32% in two multicenter studies[33,34] and in smaller studies ranged from 41-68% improvement during DBS stimulation. ADLs improved less consistently after GPi DBS. As measured by the UPDRS subscale, ADLs improved 32-38% in the two multicenter studies but were not significantly changed in five other studies reporting this outcome.

3) Improvement in motor function and levodopa-induced dyskinesias in the “on” condition

The effect upon quality of “on” time and reduction of dyskinesias was the most consistent and the most positive outcome reported among patients where DBS targeted the GPi. While changes in “on” medication UPDRS motor subscores were mixed, all studies reported improvement in duration of “on” time that was also free of dyskinesia.

In the DBS Study Group, bilateral GPi DBS was associated with an increase in percentage of time with good mobility and without dyskinesia. “On” time with good mobility and without dyskinesia increased from a mean of 28% of daily waking hours prior to implantation to 64% of daily waking hours with GPi DBS stimulation ($p<0.001$). Eight other studies reported a reduction of levodopainduced dyskinesia, measured by improvement in mean UPDRS IV subscore ranging from 33-80%.

4) Reduction in daily L-dopa dosage

It is not clear whether GPi DBS fails to permit therapeutic reductions in L-dopa dosage or allows patients' L-dopa dosage to be increased to a therapeutic level without causing dyskinesias. In 5 studies, including both multicenter studies, there was no significant change in the daily L-dopa requirement. In 3 other studies, the mean daily L-dopa dose requirement increased with GPi stimulation. Kumar and colleagues suggested that such contradictory outcomes may be attributable to stimulation of functionally distinct sites within the globus pallidus.[35]

5) Reduction in cardinal symptoms

Six studies reported moderately improved scores in tremor, rigidity and bradykinesia during the “off” medication state, but these improvements only reached statistical significance in the DBS Study Group trial and in the Burchiel et al study.

6) Duration of DBS treatment effect

In one small series of 6 patients, the effect of GPi DBS appeared to be durable for at least 2 years. Ghika and colleagues reported major improvement in mean motor scores, ADL scores and reductions in “off” time persisting beyond 2 years postoperatively, but signs of decreased efficacy started to be seen after 12 months.[36]

Neuropsychological Outcomes of Bilateral STN or GPi DBS

There was particular concern over the potential adverse effects of bilateral STN and GPi surgical procedures upon neuropsychological function. There is, however, no widely accepted standardized assessment tool such as the UPDRS for the evaluation of neuropsychological outcomes following DBS. The BCBSA TEC assessment thus provided only descriptive summaries of the neuropsychological studies. There were no studies directly comparing the effects of unilateral or bilateral stimulation and ablation and only a few studies examining the neurobehavioral outcomes of DBS stimulation.

Evidence shows that laterality of a surgically created lesion is a significant determinant of neuropsychological sequelae, such as loss of verbal and visuospatial abilities after unilateral pallidotomy.[37] Additionally, some patients pleased with pallidotomy's motor outcomes were often restricted in their ability to function properly at work or in social settings.[38] Ten studies addressing whether bilateral DBS posed this same risk were evaluated in the BCBSA TEC assessment. There was great variation among these studies in terms of design, extent to which patients were characterized at preoperative baseline, the neuropsychological and psychiatric measures employed, the frequency of and interval between examinations, the inclusion of a control group and methods used for statistical analysis.

If only the most recent publication from each medical center was considered, neuropsychological evaluation was available for 139 patients with advanced Parkinson's disease treated with DBS of either the STN or the GPi. Although studies varied in their assessment of the degree of neuropsychological risk associated with DBS, there appeared to be some consensus that the risk, while present, was minimal. Common to nearly all studies was the finding of some degree of compromise in the realm of verbal learning and/or language fluency after implantation of DBS electrodes. Noting that, in general, all surgical procedures for Parkinson's disease involving the left or both hemispheres appeared to negatively affect verbal memory, it was concluded that, since the involved nuclei are related to memory processes, some change in learning ability after these surgical procedures was to be expected.

Summary of Technology Assessment Conclusions According to TEC Criteria

TEC determined that bilateral DBS of the STN or GPi for the treatment of advanced Parkinson's disease met the following BCBSA TEC criteria: 1) the technology had final [conditional] approval from the appropriate government regulatory bodies; 2) the scientific evidence permitted conclusions concerning the effect of the technology on health outcomes; 3) the technology improved the net health outcome; 4) the technology was as beneficial as any established alternatives; and 5) the improvement was attainable outside the investigational settings.

MCAC Medical and Surgical Procedures Panel

On June 12, 2002, the Medical Surgical Procedures Panel of the Medicare Coverage Advisory Committee (MCAC) met to discuss the topic of DBS for Parkinson's disease. Included in this panel meeting were recognized experts in clinical and academic medicine, health services research, Parkinson's disease and movement disorders, neurosurgery and neurology. During the course of the panel meeting, the panel heard public testimony and had presentations from the requestor, CMS, FDA and Medtronic. The complete minutes and transcripts of the meeting are available on CMS's website.[39]

The following voting questions were directed to the panel:

- *Is the evidence adequate to determine the clinical effectiveness of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) for a well-defined set of Medicare patients with Parkinson's disease?*

  If the evidence is adequate, what is the size, if any, of the overall health effect of bilateral STN DBS for those patients?
- *Is the evidence adequate to determine the clinical effectiveness of bilateral internal globus pallidus (GPi) DBS for a well-defined set of Medicare patients with Parkinson's disease?*

  If the evidence is adequate, what is the size, if any, of the overall health effect of bilateral GPi DBS for those patients?
- *Is the evidence adequate to determine the clinical effectiveness of unilateral thalamic DBS for essential tremor and/or Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease?*

  If the evidence is adequate, what is the size, if any, of the overall health effect of unilateral thalamic DBS for essential tremor and/or Parkinsonian tremor for those patients?

The overall health effect was as defined under categories of effectiveness in the MCAC interim guidelines in Appendix B.

The following discussion questions were directed to the panel:

- *Available clinical evidence evaluates bilateral STN or GPi DBS in early onset Parkinson's disease patients. Can these results be generalized to late onset advanced Parkinson's disease patients?*
- *For coverage purposes, should Medicare patients be considered candidates for unilateral thalamic or bilateral STN or GPi DBS only if their characteristics closely match those of the patients included in the available studies?*
- *DBS in the clinical literature is performed by highly trained providers at experienced facilities. Should facility and provider criteria to perform DBS in Medicare patients be part of any positive coverage decision?*

Panel Conclusions for Unilateral Thalamic DBS

The MCAC panel voted that the evidence was adequate to determine the clinical effectiveness of unilateral thalamic [VIM] DBS for essential tremor and Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease.

Prior to voting on levels of effectiveness, the panel discussed the differences between “breakthrough technology” and “more effective.” Some panelists stated that in some ways this technology may have represented a breakthrough, as in a major advance in treatment, but it did not rise to the level of standard of care. They also felt that it had more than small effects, as in the definition of “more effective” provided by the Executive Committee. Following this discussion, the panel voted unanimously to temporarily create a new category of effectiveness, falling between “breakthrough” and “more effective.” They voted in favor of a statement that it improves health outcomes by a substantial margin as compared with established services or medical items.

Panel Conclusions for Bilateral STN and GPi DBS

The panel voted that the evidence was adequate to determine the clinical effectiveness of bilateral STN DBS and bilateral GPi DBS for a well-defined set of Medicare patients with Parkinson's disease. The panel likewise concluded that both STN and GPi DBS improve health outcomes by a substantial margin.

Panel Discussion

The panel noted that tremor may be unilateral or bilateral or one side may predominate in ET and PD patients with disabling tremor. The panelists, therefore, also discussed the utility of both unilateral and bilateral (VIM) thalamic DBS. Neurosurgeon panelist Dr. Burchiel disagreed with the BCBSA assessment's statement that bilateral thalamic stimulation was not done because of untoward effects on oropharyngeal musculature, dysphasia and dysarthria. While difficult to ascertain from the literature whether the bilateral procedures had been done simultaneously or sequentially (staged), in practice it was noted that after having unilateral DBS for the side predominantly affected by tremor, the patient often responds so well that he or she seeks the procedure on the other side. In these cases, simultaneous implantation may not be as warranted or as desirable as staged bilateral thalamic DBS. Neurosurgeon panelist Dr. Follett strongly concurred that bilateral thalamic stimulation is done quite effectively, that actual practice today deals with bilateral stimulation, and that it would do some of their patients [with bilateral tremor] a real disservice to restrict thalamic DBS to unilateral applications.

A number of panelists expressed concern that the skill and training of practitioners may affect health outcomes. In response to a question regarding marketing of the procedures, Medtronic stated that the decision to recommend treatment is reached through a team approach for each patient, and that any physician doing the procedure would be adequately trained. A concern was also raised regarding whether the patient population benefiting from DBS would be Medicare beneficiaries. After discussion, it was the consensus of the panel that although patients may not be 65 years of age when they have the need for the treatment, they would probably qualify for Medicare coverage by reason of their disability. Therefore, DBS would affect a well-defined segment of the Medicare population.

In addition to discussion regarding the age distribution for DBS results, discussion also ensued regarding additional Medtronic data provided to the panel regarding DBS complications under and over the age of 65 years (See Appendix C). Statistically significant differences were noted for cardiovascular disorders, confusion, paresis, hemiplegia and intracranial hemorrhage, including that hemiplegia (a very significant adverse effect) occurred almost five times as frequently in people over the age of 65 as in people under the age of 65. Overall, while the data submitted for age stratification was felt to be limited, the panel acknowledged that the direction of the evidence appeared to be for continued benefit, but with increased risks of the procedure with advancing age. The MCAC panel also discussed the difficulty in identifying early onset versus late onset PD patients, as well as the duration of disease, severity of disease and response to medications further complicating generalizations of study results from one group to the other.

In conclusion, the MCAC panel generally agreed that as part of any coverage decision there should be patient, provider and facility criteria for performing DBS in Medicare patients. The panel reiterated the consensus that although there should be criteria, the MCAC panel was not the body to determine those criteria.

On September 25, 2002, the MCAC Executive Committee (EC) met to discuss and ratify the findings of the Medical and Surgical Procedures panel. In discussing the panel's findings, the EC added language to the panel recommendation better defining the meaning of a “well-defined set of Medicare patients with Parkinson's disease.” The committee approved the following language to describe this group: “patients who have reached maximum benefit from medical treatment and continue to have unacceptable symptoms from the disease or increasing side effects from medications.” The EC voted to approve the amended recommendation, as well as the addition of “substantially more effective” to the MCAC categories of effectiveness.

Professional Society Guidelines

A report from the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated surgery for PD based on the published literature up to December 1998. The report concluded that surgery for PD was “rapidly becoming an important therapeutic consideration in the management of medication-resistant disease based on a strong consensus of Class III evidence, i.e., provided by nonrandomized, historical controls or case series.” DBS of the thalamus, pallidum and subthalamic nucleus carried a recommendation, at that time, of “investigational”, but new knowledge was expected to accrue rapidly.[40] No new or revised professional guidelines were subsequently identified. The next section of this decision memorandum presents current expert opinion submitted by both the neurological and neurosurgical societies.

Expert Opinion

American Academy of Neurology (AAN)

Dr. David Charles, speaking on behalf of the AAN, addressed the June 2002 MCAC panel to recommend a national policy coverage decision for the application of DBS for the treatment of tremor and Parkinson's disease.

Dr. Marc Nuwer, Chairman of the AAN's Medical Economics and Management Committee, provided a written statement for the MCAC panel, which included the following comments: “As enthusiastic as the Academy is about the demonstrated effectiveness of DBS, we stress that pharmacotherapy is the first line of defense against Parkinson's disease. DBS has been developed and tested specifically for those advanced levodopa-responsive Parkinson's patients with severe symptoms who have been unresponsive to drug therapy or who have developed a serious intolerance to the drug treatment. These are people with the most acute symptoms and most acute lack of treatment options. For these patients, DBS is an efficient solution that will improve both their treatment of symptoms and quality of life.”

American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)

Dr. Frederick Lenz, speaking on behalf of AANS/CNS, addressed the June 2002 MCAC panel to explain the history of DBS and targeting of the thalamus, GPi or STN. Dr. Lenz noted that medications and stimulators are adjusted simultaneously in Parkinson's patients and, in carrying out these procedures, it was essential to have a movement-disorder neurologist determine each patient's diagnosis, decide whether maximal medical therapy had been employed, and adjust the stimulators.

In its written comments for the MCAC panel, the AANS/CNS noted that the BCBSA TEC assessment published in January 2002 had stated that “Because it is associated with a higher incidence of speech, swallowing, and cognitive dysfunction, bilateral DBS of the VIM is seldom performed.” The AANS/CNS responded by saying: “We disagree with this statement, as many centers perform bilateral VIM DBS for patients with bilateral tremor[41,42]. Although between 3050% of patients will initially have side effects from stimulation, the adjustability and reversibility of the therapy allow virtually all patients to achieve some measure of tremor control with minimal or controllable side effects. If unacceptable side effects persist, the DBS system can be deactivated. DBS therefore represents the only option for patients with severe bilateral tremor. However, most investigators now agree that the results from STN stimulation are superior for Parkinson's disease, and the side effect profile less. Thalamic DBS should thus usually be reserved for Essential Tremor or other non-Parkinsonian tremor disorders, although it may still have a role in rare Parkinsonian patients whose sole disabling symptom is tremor.”

The AANS/CNS concluded that DBS has been shown to be “a safe and effective procedure for medically intractable Parkinson's disease and other movement disorders, when performed in appropriate centers." Detailed recommendations (see Appendix D) were also made by the AANS/CNS regarding general indications for DBS, specific indications by target site (VIM thalamus, STN and GPi), contraindications for DBS, and technical criteria for performing DBS.

Ongoing Clinical Trials

Definitive determination of which stimulation target, the STN or GPi, provides most effective therapy requires a well-designed randomized clinical trial. Such a trial, the Veterans' Administration and NIH's National Institute of Neurological Disorders and Stroke (VA/NINDS) Cooperative Trial, involving six Parkinson's disease centers and their university affiliates, started in 2002 and plans to enroll a total of 300 patients. Patients will be randomized to one of two groups, either immediate DBS surgery or delayed DBS surgery after a six month trial of best medical management. Each surgical group will then be further randomized to either STN or GPi targeting, and all patients will be followed for two years.

CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a)(1)(A).

Our analysis focused on the following questions, posed to the June 2002 MCAC panel and subsequently utilized in CMS's decision-making process:

Is the evidence adequate to determine the clinical effectiveness of bilateral STN DBS for a well-defined set of Medicare patients with Parkinson's disease?

Key outcomes from the evidence reviewed consistently demonstrated that bilateral STN DBS relieves certain symptoms of Parkinson's disease, particularly motor fluctuations, “off' state immobility and “on” state dyskinesias. STN DBS also allows or sometimes necessitates reduction in the L-dopa or equivalent medication dosage. CMS concludes that the number of consecutively treated STN DBS patients published throughout the literature, the consistency of the findings across studies, and the magnitude of clinical improvements observed on standardized, neurological rating scales have provided adequate evidence for the effectiveness of bilateral STN DBS *in the selected patient populations studied*.

For neuropsychological outcomes associated with STN as well as GPi DBS, CMS concludes that the significant motor benefits achieved with bilateral DBS may be accompanied by some adverse neurocognitive effects. These are not comparable, however, to the unacceptably high risks associated with bilateral pallidotomy and it appeared that bilateral DBS's negative impact upon neurobehavioral function was not as clinically meaningful to most patients as the potential motor improvement. For most investigators and patients, the motor benefits of DBS thus appeared to outweigh the neuropsychological risks.

A surgical alternative for patients with medically refractory Parkinson's disease is pallidotomy, but there were no studies directly comparing chronic bilateral STN DBS with pallidotomy. Pallidotomy, however, is limited to a unilateral procedure because of an unacceptably high risk of adverse neuropsychological outcomes if performed bilaterally. The fact that STN DBS can be offered bilaterally is thus advantageous, since PD symptoms most often affect both sides of the body. Unlike the pallidal ablative procedure, STN DBS also has the advantage of being adjustable and reversible (the electrode can be removed).

Patients with advanced, asymmetric PD may initially require only unilateral STN or GPi DBS. These PD patients include those with severe asymmetric tremor who can be effectively treated with unilateral thalamic or STN DBS, as well as those with severe unilateral dyskinesias who can be treated with unilateral GPi DBS. Krause and colleagues noted that STN DBS suppressed tremor as effectively as thalamic VIM DBS and (contrary to thalamic VIM stimulation) caused no tremor rebound when stimulation was switched off. STN DBS could thus be as effective, or possibly even the preferred target, for some patients with either unilateral or bilateral tremor-dominant PD.[43]

CMS recognizes that there may occasionally be patients with advanced, asymmetric PD who initially require only unilateral STN or GPi DBS. Such patients would include those with severe asymmetric tremor of PD effectively treated with either unilateral thalamic or STN DBS, as well as those patients with severe unilateral dyskinesias that can be treated with unilateral GPi DBS.

Is the evidence adequate to determine the clinical effectiveness of bilateral GPi DBS for a well-defined set of Medicare patients with Parkinson's disease?

Key outcomes from the evidence reviewed consistently demonstrated that bilateral GPi DBS results in clinically important improvement in both motor symptoms of PD and reduction in levodopainduced dyskinesias. However, whereas STN DBS permitted significant reductions in daily L-dopa dosage, GPi STN showed no significant change or in some studies showed an increase in the mean daily L-dopa requirement. CMS concludes that the number of consecutively treated GPi DBS patients published throughout the literature, the consistency of the findings across studies, and the magnitude of clinical improvements observed on standardized, neurological rating scales have provided adequate evidence for the effectiveness of bilateral GPi DBS in the selected patient populations studied.

While it is possible that GPi DBS may be preferable to STN DBS particularly for patients in whom levodopa-induced dyskinesia is the primary obstacle to an otherwise optimal drug effect, long-term reduction of L-dopa dosage in the STN group has also been reported to eventually lead to a reduction in dyskinesia similar to that achieved in the GPi group. Definitive determination of which stimulation target provides the most effective therapy awaits the results of the ongoing, randomized VA/NINDS Cooperative Trial.

A surgical alternative for patients with medically refractory Parkinson's disease is pallidotomy; but just as for STN DBS, there are no studies directly comparing chronic bilateral GPi DBS with unilateral pallidotomy. Unlike the pallidal ablative procedure, stimulation of the GPi has advantages of being reversible and adjustable; and the fact that stimulation of the GPi can be offered bilaterally is again advantageous, since Parkinson's disease most often affects both sides of the body.

Is the evidence adequate to determine the clinical effectiveness of unilateral thalamic DBS for essential tremor and/or Parkinsonian tremor for a well-defined set of Medicare patients with Parkinson's disease?

Several large multicenter series describe symptomatic improvement of tremor in both Parkinson's and essential tremor patients treated with unilateral thalamic (VIM) DBS.[44,45,46] While data was generally pooled across centers and the effect of unilateral and bilateral implantation was not always clearly stated, additional sizeable clinical series with consistent results have since been published evaluating the results and adverse events of both unilateral and bilateral thalamic (VIM)

DBS for refractory Parkinson's disease and essential tremor.[47,48] CMS concludes that consistent and significant improvements in tremor control and other functional outcomes have provided adequate evidence for the effectiveness of unilateral and bilateral thalamic (VIM) DBS *in the selected patient populations studied*. Although none of the thalamic studies were performed in a randomized fashion, basic inclusion criteria were consistent across studies, suppression of tremor was the primary outcome measure, and preoperative baseline and on stimulation/off stimulation measures served as controls.

A comparison between unilateral and bilateral placement for thalamic DBS also recently showed bilateral thalamic DBS to be more effective than unilateral DBS at controlling bilateral appendicular and midline tremors of ET and tremor-dominant PD patients[49] and simultaneous bilateral thalamic implantation or complementary implantation following prior contralateral thalamotomy was reported not to have induced any of the neuropsychological deficits associated with bilateral thalamotomy.[50] Additionally, following bilateral thalamic (VIM) DBS, side effects such as reversible dysarthria under stimulation may in fact be tolerable to some patients and have been reported to be preferable to medically refractory tremor severely impairing routine daily activities.[51]

Available clinical evidence evaluates bilateral STN or GPi DBS in early onset Parkinson's disease patients. Can these results be generalized to late onset advanced Parkinson's disease patients?

CMS recognizes that it is frequently difficult to distinguish early onset from late onset PD patients. Some patients may have slowly progressing, early or mild disease continuing for years prior to the diagnosis of PD, whereas other patients with access to a neurologist specializing in movement disorders may have earlier diagnosis of their disease.

No direct comparison study of DBS in early onset versus late onset PD patients was identified, but one bilateral DBS study did specifically select only early onset PD patients. All patients in that study's comparison of STN and GPi DBS were selected for PD onset before the age of 40 years because those patients were said to generally suffer from the most severe motor complications of L-dopa (dyskinesias and motor fluctuations) and have little comorbidity.[52] Krack and colleagues also hypothesized that young onset PD patients seemed to be the best surgical candidates because their symptoms were highly L-dopa responsive, and the study's mean duration of disease was 16 years and mean age at surgery was 51 years. The remaining literature largely, though not exclusively, examined the outcomes of DBS in younger onset patients. The mean age at surgery in the commonly referenced DBS Study Group was 59.6 years for the STN group and 55.7 years for the GPi group.

According to testimony before the FDA's Neurological Devices Advisory Committee, the majority of PD patients typically have their onset of disease in the late fifth or early sixth decade, and become significantly refractory to medication in their 60s and 70s.[53] Furthermore, the direction of the evidence (including Medtronic's limited supplemental age stratification data) was for decreased though continued benefit, but increased procedural risks with advancing age. There were statistically significant increases in the rate of complications, especially intracranial hemorrhage and neurologic deficits, for patients over 65 years of age. This was also corroborated by Benabid et al, who emphasized that the complications related to DBS increase exponentially with chronological age.[54] In fact, throughout the published literature, the selection of younger PD patients and exclusion of older Medicare or late onset PD patients tends to maximize the effect size of DBS, while minimizing its risks.

While agreeing that existing data for late onset PD patients was inadequate, expert opinion from the MCAC panel nonetheless suggested that the more critical issue was patients' duration and severity of disease. CMS concludes that while there may be benefit for selected late onset Medicare patients, generalization of currently published DBS results to these late onset advanced PD patients is only feasible when duration of disease, severity of disease, response to medications, comorbidities and overall physiological status are comparable to the patient inclusion and exclusion criteria in the available studies.

For coverage purposes, should Medicare patients be considered candidates for unilateral thalamic or bilateral STN or GPi DBS only if their characteristics closely match those of the patients included in the available studies?

While retrospective case series for both unilateral and bilateral DBS have provided compelling evidence for selected populations, no large well-designed prospective study or RCT has adequately evaluated the risks, benefits and optimal target selection for DBS in a representative sample of elderly Medicare patients. Additionally, the long-term safety and effectiveness of DBS therapy have not been established and FDA's determinations of safety and effectiveness are explicitly limited to the populations studied. In particular, for use in specific populations, current labeling precautions include that safety and effectiveness have not been established for patients with neurological disease origins other than ET or idiopathic PD, with a previous surgical ablation procedure, over the age of 75 years, with dementia, with coagulopathies or with moderate to severe depression.[55] CMS remains concerned regarding the external validity or generalization of the risks and benefits of DBS for Medicare patients and concludes that Medicare patients be considered candidates for thalamic, STN or GPi DBS only if their clinical characteristics closely match the patient selection criteria in the published literature.

Specifically, for unilateral or bilateral thalamic (VIM) DBS, ET and tremor-dominant PD patients must have marked disabling tremor refractory to optimal medical therapy. Likewise, for unilateral or bilateral STN or GPi DBS, PD patients must have advanced idiopathic PD, be L-dopa responsive with clearly defined “on” periods, and have persistent disabling symptoms refractory to optimal medical therapy. Patients must not have significant cognitive impairment, dementia or depression; current psychosis, alcohol abuse or other drug abuse; or significant medical, surgical, neurologic or orthopedic co-morbidities - any of which could be worsened by or could complicate, diminish the effectiveness of, or otherwise interfere with a patient's willingness and ability to cooperate during the operative procedures and/or the postoperative evaluations and adjustments of medications and stimulator settings. Patients must not have a stroke, tumor or vascular malformation causing their movement disorder, and patients must not have had prior movement disorder surgery within the affected basal ganglion. In all circumstances, the patient's symptoms must be sufficiently and significantly disabling to warrant DBS, yet symptoms must not be so disabling or overall health status so impaired that DBS would be unlikely to provide any functional benefit.

Additionally, patients who undergo DBS implantation should not be exposed to any form of diathermy (deep heat treatment including shortwave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely affect the DBS system or adversely affect the brain around the implanted electrodes. DBS should be performed with extreme caution in patients with cardiac pacemakers or other electronically controlled implants which may adversely affect or be affected by the DBS system.

DBS in the clinical literature is performed by highly trained providers at experienced facilities. Should facility and provider criteria to perform DBS in Medicare patients be part of any positive coverage decision?

Regarding facility criteria, CMS concludes that medical centers where DBS is to be performed must have brain imaging equipment (MRI and/or CT) for preoperative stereotactic localization and targeting of the surgical site(s), operating rooms with all necessary equipment for stereotactic surgery, and necessary support services for the intraoperative and postoperative care of all Medicare DBS patients.

Regarding provider criteria, CMS acknowledges that the degree of benefit from DBS is clearly reliant on the proper selection of patients and accuracy in targeting, and that selected centers with experienced operators have reported excellent results for patients with severe Parkinson's symptoms refractory to L-dopa. CMS thus concurs with the AANS/CNS recommendation that DBS procedures should only be performed by neurosurgeons skilled in the techniques of stereotactic and functional surgery, who have been trained in the performance of DBS procedures, and who have been credentialed by their institutions as competent to perform these procedures. CMS also concurs with the MCAC panel that physicians specializing in movement disorders must be involved in the diagnosis, selection and post-procedure care of DBS patients. Operative teams must be experienced with target localization and electrode implantation, as well as the operational and functional characteristics of the device.

Decision

Effective upon implementation of our national coverage determination, Medicare will cover *unilateral or bilateral thalamic VIM DBS* for the treatment of essential tremor (ET) and/or Parkinsonian tremor and *unilateral or bilateral STN or GPi DBS* for the treatment of Parkinson's disease only under the following conditions:

1. Medicare will only consider DBS devices to be reasonable and necessary if they are Food and Drug Administration (FDA) approved devices for DBS or devices used in accordance with FDA approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.

2. For thalamic VIM DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

a.

Diagnosis of essential tremor (ET) based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form

b.

Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.

c.

Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

3.

For STN or GPi DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

a.

Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).

b.

Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.

c.

L-dopa responsive with clearly defined “on” periods.

d.

Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling “off” periods) despite optimal medical therapy.

e.

Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

DBS is not reasonable and necessary and is not covered for ET or PD patients with any of the following:

1. Non-idiopathic Parkinson's disease or “Parkinson's Plus” syndromes.
2. Cognitive impairment, dementia or depression which would be worsened by or would interfere with the patient's ability to benefit from DBS.
3. Current psychosis, alcohol abuse or other drug abuse.
4. Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
5. Previous movement disorder surgery within the affected basal ganglion.
6. Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.

Patients who undergo DBS implantation should not be exposed to diathermy (deep heat treatment including shortwave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely affect the DBS system or adversely affect the brain around the implanted electrodes.

DBS should be performed with extreme caution in patients with cardiac pacemakers or other electronically controlled implants which may adversely affect or be affected by the DBS system.

For DBS lead implantation to be considered reasonable and necessary, providers and facilities must meet all of the following criteria:

1.

Neurosurgeons must: (a) be properly trained in the procedure; (b) have experience with the surgical management of movement disorders, including DBS therapy; and (c) have experience performing stereotactic neurosurgical procedures.

2.

Operative teams must have training and experience with DBS systems, including knowledge of anatomical and neurophysiological characteristics for localizing the targeted nucleus, surgical and/or implantation techniques for the DBS system, and operational and functional characteristics of the device.

3.

Physicians specializing in movement disorders must be involved in both patient selection and post-procedure care.

4.

Hospital medical centers must have: (a) brain imaging equipment (MRI and/or CT) for pre-operative stereotactic localization and targeting of the surgical site(s); (b) operating rooms with all necessary equipment for stereotactic surgery; and (c) support services necessary for care of patients undergoing this procedure and any potential complications arising intraoperatively or postoperatively.

Since long-term safety, effectiveness and optimal targeting for DBS have not been established, CMS will review the appropriateness of Medicare coverage as pertinent new evidence becomes available. This review will include clinical follow-up and targeting information from the ongoing, randomized VA/NINDS Cooperative Trial comparing best medical therapy with DBS of the STN and GPi for PD, as well as longer term clinical results from mandatory annual progress reports and final report to the FDA of Medtronic's bilateral DBS PMA postapproval study.

Appendices [PDF, 2MB]

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1 Tintner and Jankovic (2002)

2http://www.medtronic.com/neuro/parkinsons/product.html

3http://www.fda.gov/cdrh/pdf/p960009.pdf

4 http://www.fda.gov/cdrh/pdf/p960009s7.html

5 Fahn, Tolosa, Marin (1993)

6 BCBSA TEC (1997)

7 Koller et al (1997)

8 Benabid et al (1996)

9 Alesch et al (1995)

10 http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3273t1.pdf

11 BCBSA TEC (1997)

12 Krauss et al (2001)

13 Limousin et al (1999)

14 Ondo et al (2001)

15 DBSPDSG (2001)

16 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1a.pdf

17 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1b.pdf

18 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1c.pdf

19 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1d.pdf

20 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1b.pdf

21 http://www.cms.hhs.gov/coverage/8b3-jjj1.asp

22 DBSPDSG (2001)

23 Benabid et al (2000)

24 Burchiel et al (1999)

25 Broggi et al (2001)

26 Rodriquez-Oroz et al (2000)

27 Benabid et al (2000)

28 Benabid et al (2000)

9 Rodriguez-Oroz et al (2000)

30 Kumar et al (2000

31 DBSPDSG (2001)

32 Burchiel et al (1999)

33 Kumar et al (2000)

34 DBSPDSG (2001)

35 Kumar et al (2000)

36 Ghika et al (1998)

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38 Stebbins et al (2000)

39 http://www.cms.hhs.gov/coverage/8b3-jjj1.asp

40 Hallett et al (1999)

41 Krauss et al (2001)

42 Taha et al (1999)

43 Krause et al (2001)

44 Benabid et al (1996)

45 Krauss et al (2001)

46 Limousin et al (1999)

47 Krauss et al (2001)

48 Limousin et al (1999)

49 Ondo et al (2001)

50 Benabid et al (1996)

51 Alesch et al (1995)

52 Krack et al (1998)

53 http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3606t1a.pdf

54 Benabid et al (2000)

55 http://www.fda.gov/cdrh/pdf/p960009s7.html

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